Tetrahedron Letters 55 (2014) 5454–5457

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of α-phthalimido-α′-dithiocarbamato propan-2-ols via a one-pot, three-component epoxide ring-opening in water

Azim Ziyaei Halimehjani *, Seyyed Emad Hooshmand, Elham Vali Shamiri

Faculty of Chemistry, Kharazmi University, 49 Mofateh St., Tehran, Iran

ARTICLE INFO

Article history:
Received 19 May 2014
Revised 19 July 2014
Accepted 6 August 2014
Available online 14 August 2014

Keywords:
Dithiocarbamate
Phthalimide
Propan-2-ols
Water
Catalyst-free

ABSTRACT

Regioselective ring-opening of the *N*-(2,3-epoxypropyl)phthalimide with in situ prepared dithiocarbamic acid in water is reported for the synthesis of a new family of α-phthalimido-α′-dithiocarbamato propan-2-ols. The present method is simple, EtOAc is used for work-ups and affords excellent yield of products.

In recent years, many attempts have been made to synthesize substituted α,α′-substituted propan-2-ol derivatives. These compounds demonstrate various pharmacological activities in the areas of drug development such as antibacterial, antimicrobial, antiplasmodial, antioxidant, and antimalarial agents.[1] Moreover, they often constitute key synthons in the preparation of biologically active compounds.[2] Among the various types of α,α′-substituted propan-2-ols, it is well documented that the α-amino-α′-dithiocarbamato propan-2-ols (Fig. 1) have biological applications as spermicidal, antifungal, and antitrichomonas agents and as safe pesticides.[3] Also, these compounds can be considered as glycerol analogs with a sulfur atom in position 1 and nitrogen atom in position 3 which have been confirmed to have various biological activities.[4] The dithiocarbamate group is a valuable pharmacophore that induces various biological activities when incorporated in a particular structure.[3,5] They constitute a large family of herbicides, fungicides, and pesticides in agriculture and several compounds of this category such as Zineb, Maneb, Nabam, ziram, and Ferbam have been commercialized.[6] Also, they were extensively used as sulfur vulcanization agents in rubber manufacture,[7] and radical chain transfer agents in reversible addition-fragmentation chain-transfer (RAFT) polymerizations.[8] Furthermore, they have been used as versatile synthetic intermediates for the preparation of thioureas,[9] isothiocyanates,[10] 2-imino-1,3-dithiolanes,[11] cyanamides,[12] heterocyclic rings,[13] the protection of aldehydes,[14] amide bond formation,[15] and protection of amino groups in peptide synthesis.[16] The classical synthesis of dithiocarbamates involves the use of thiophosgene and an isothiocyanate which are costly and toxic reagents.[17] Several efficient procedures for the synthesis of these compounds have been developed by our group and others to overcome most of the drawbacks associated with the classical methods by using the direct condensation of amines, carbon disulfide, and electrophiles such as alkyl halides, activated alkenes, carbonyl compounds, and epoxides.[18]

The phthalimide group is present as the pharmacophoric moiety in the structure of many biologically active compounds. Compounds containing the phthalimide group have shown anti-inflammatory and anti-angiogenic properties, and have been introduced as potential candidates in the treatment of HIV and cancer.[19] The phthalimide fungicides such as captan, captafol, and folpet are

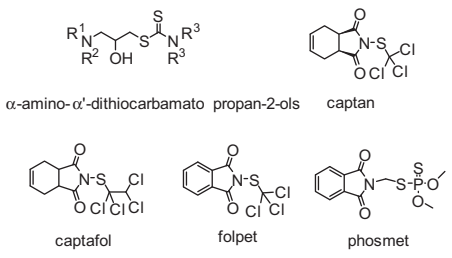


Figure 1. Structures of phthalimide- and dithiocarbamate-based biologically active compounds.

* Corresponding author. Tel.: +98 (21)88848949; fax: +98 (21)88820992.
E-mail address: ziyaei@khu.ac.ir (A.Z. Halimehjani).

http://dx.doi.org/10.1016/j.tetlet.2014.08.017
0040-4039/

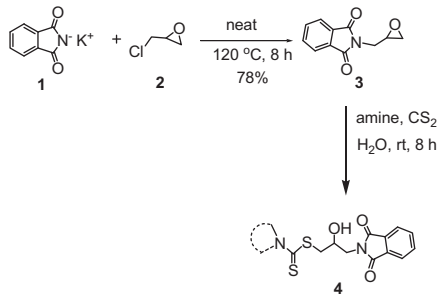
the most applied surface protectants for control of plant pathogenic fungi.[20] In addition, phosmet is a phthalimide-derived organophosphate insecticide used on plants and animals (Fig. 1).[21]

These observations prompted us to introduce an efficient procedure for the synthesis of a new family of α,α′-substituted propan-2-ols containing both a dithiocarbamate and a phthalimide moiety, as potential biologically active compounds, via a one-pot, three-component ring-opening of epoxides in water.

The use of hazardous and toxic solvents in chemical processes is considered to be a very important problem for the health and safety of workers, and environmental pollution. In addition, although the use of catalysts for organic transformations has several advantages, usually these processes need extra steps for producing the catalyst or removing the catalyst from the reaction medium. For this purpose, many reactions are designed to proceed cleanly and efficiently in water, in ionic liquids, in green solvents such as fluorinated solvents and polyols, and under solvent-free conditions without using catalysts, which are in agreement with the goals of green chemistry.[22] In continuation of our research toward the development of green organic chemistry using water as the reaction medium or performing organic transformations under solvent-free and catalyst-free conditions,[23] herein we report an efficient, novel, and environmentally benign procedure for the synthesis of α-phthalimido-α′-dithiocarbamato propan-2-ols via the catalyst-free regioselective ring-opening of *N*-(2,3-epoxypropyl)phthalimide with in situ prepared dithiocarbamic acids in water.

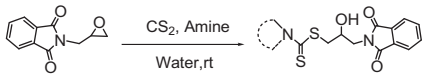
We began our investigation on the synthesis of *N*-(2,3-epoxypropyl)phthalimide (**3**) by reacting potassium phthalimide (**1**) and epichlorohydrin (**2**) under solvent-free conditions as described in the literature.[24,25] Next, a one-pot, three-component reaction of an amine, CS_2, and the epoxide (**3**) was designed for obtaining the title products. Different reaction conditions were examined for this process; mixing the amine (2.5 mmol) and CS_2 (3 mmol) in water at room temperature for 0.5 h to give the corresponding dithiocarbamic acid and then addition of the epoxide (**3**) and additional stirring for eight hours represents the optimum conditions (Scheme 1). No catalyst is needed for this reaction. Although the reaction gave acceptable yields in organic solvents, the yield was higher in water in shorter reaction times.

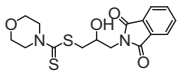
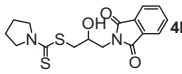
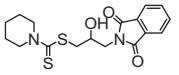
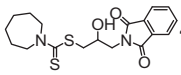
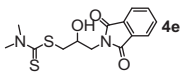
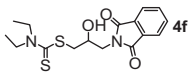
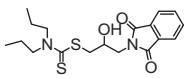
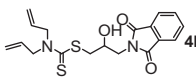
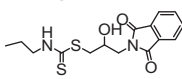
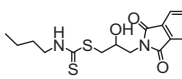
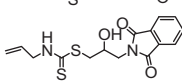
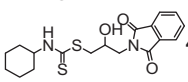
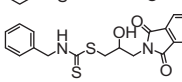
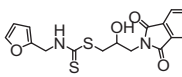
With optimized conditions in hand, the scope of this reaction was investigated using different primary and secondary aliphatic amines (Table 1). Secondary amines such as pyrrolidine, piperidine, dimethylamine, diethylamine, azepine, dipropylamine, diallyl amine, and morpholine all gave excellent yields. Primary amines such as propylamine, butylamine, allylamine, cyclohexylamine, furfurylamine, and benzylamine reacted equally well in this protocol. Hindered amines such as *tert*-butylamine and dicyclohexylamine did not give any products and the starting materials were recovered. Aromatic amines were not suitable starting materials for this reaction. In addition, *N*,*N*-dimethylethylenediamine gave no reaction under similar conditions.



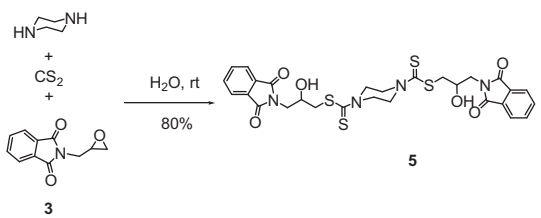
Scheme 1. One-pot three-component route for the synthesis of α-phthalimido-α′-dithiocarbamato propan-2-ols.

Table 1
Synthesis of α-phthalimido-α′-dithiocarbamato propan-2-ols[26]



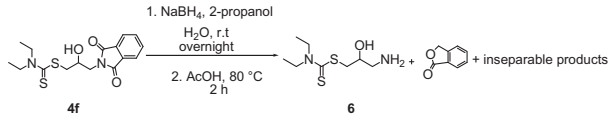
Entry	Amine	Product	Yield (%)[a]
1			92
2			95
3			98
4			90
5			86
6			98
7			79
8			86
9			84
10			78
11			84
12			80
13			86
14			82

[a] Isolated yield.

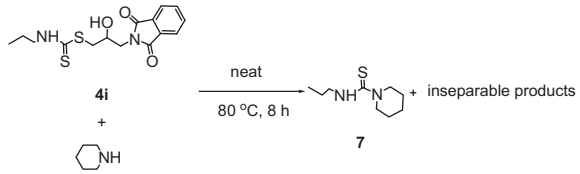


Scheme 2. Synthesis of bisdithiocarbamate **5**.

It has been well demonstrated that the fungicidal activity of a compound can be improved by increasing the number of dithiocarbamate moieties in the structure.[4c,4d] For this purpose, bis (dithiocarbamate) (**5**) was prepared in 80% yield via the one-pot



Scheme 3. Deprotection of the amino group in (**4f**) using the Osby method.



Scheme 4. Reaction of (**4i**) with piperidine.

three-component reaction of piperazine with carbon disulfide and epoxide (**3**) in water (Scheme 2).

Having successfully synthesized α,α′-substituted propan-2-ols, we focused our attention on the removal of the phthalimide group to give the α-amino α′-dithiocarbamato propan-2-ols. For this purpose, we tried to remove the phthalimide group using the Ing-Manske exchange reaction,[27] but no desired product was obtained. An alternative protocol was applied for this reaction using $NaBH_4$ in isopropanol (Osby method).[28,29] We found that under these conditions, the desired product (**6**) was obtained in 30% yield along with other inseparable products (Scheme 3). The target compound (**6**) could furnish bisdithiocarbamate of glycerol with a sulfur atom in position 1 and nitrogen atom in position 3.[4a,4b]

In addition, we attempted to synthesize an α-phthalimido α′-thiopropan-2-ol via the reaction of (**4i**) with piperidine under solvent-free conditions at 80 °C (Scheme 4).[9a] Although the thiourea (**7**) was obtained in pure form,[30] unfortunately we did not obtain the corresponding α-phthalimido α′-thiopropan-2-ol.

In conclusion, we have described a novel, simple, and highly efficient procedure for the synthesis of 3-(1,3-dioxoisoindolin-2-yl)-2-hydroxypropylalkyl carbamodithioate derivatives via a one-pot, three-component reaction of an amine, CS_2, and epoxide (**3**) in water under catalyst-free conditions. High yields, simple reaction conditions, and completely regioselective reactions are advantages of this process. Water may play a dual role as the solvent and the catalyst in this reaction by activation of the epoxy group via hydrogen bonding. In addition, the presence of the phthalimide, dithiocarbamate, and alcohol functionalities in these compounds may have synergic effects to provide a new family of compounds with interesting biological activities in agriculture or pharmaceutical industry.

Acknowledgement

We are grateful to the Faculty of Chemistry of Kharazmi University (formerly Tarbiat Moallem University) for supporting this work.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.017.

References and notes

1. Singh, G. S.; Mollet, K.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2013**, *113*, 1441–1498.
2. (a) Martinez, F.; Del Campo, C.; Sinisterra, J. V.; Llama, E. F. *Tetrahedron: Asymmetry* **2000**, *11*, 4651–4660; (b) Onishi, T.; Nakano, T.; Hirose, N.; Nakazawa, M.; Izawa, K. *Tetrahedron Lett.* **2001**, *42*, 5887–5890; (c) Hamada, T.; Torii, T.; Onishi, T.; Izawa, K.; Ikariya, T. *J. Org. Chem.* **2004**, *69*, 7391–7394.
3. Kiran Kumar, S. T. V. S.; Kumar, L.; Sharma, V. L.; Jain, A.; Jain, R. K.; Maikhuri, J. P.; Kumar, M.; Shukla, P. K.; Gupta, G. *J. Med. Chem.* **2008**, *43*, 2247–2256.
4. (a) Len, C.; Postel, D.; Ronco, G.; Villa, P.; Goubert, C.; Jeufrault, E.; Mathon, B.; Simon, H. *J. Agric. Food Chem.* **1997**, *45*, 3–6; (b) Len, C.; Boulogne-Merlot, A.; Postel, D.; Ronco, G.; Villa, P. *J. Agric. Food Chem.* **1996**, *44*, 2856–2858; (c) Rafin, C.; Veignie, E.; Postel, M. S.; Len, C.; Villa, P.; Ronco, G. *J. Agric. Food Chem.* **2000**, *48*, 5283–5287; (d) De Sousa, R.; Thurier, C.; Len, C.; Pouilloux, Y.; Barrault, J.; Jérôme, F. *Green Chem.* **2011**, *13*, 1129–1132.
5. (a) Kumar, L.; Lal, N.; Kumar, V.; Sarswat, A.; Jangir, S.; Bala, V.; Kumar, L.; Kushwaha, B.; Pandey, A. K.; Siddiqi, M. I.; Shukla, P. K.; Maikhuri, J. P.; Gupta, G.; Sharma, V. L. *Eur. J. Med. Chem.* **2013**, *70*, 68–77; (b) Tripathi, R. P.; Khan, A. R.; Setty, B. S.; Bhaduri, A. P. *Acta Pharm.* **1996**, *46*, 169–176; (c) Ates, O.; Kocabalkanli, A.; Cesur, N.; Otuk, G. *Il Farmaco* **1998**, *53*, 541–544; (d) Nofal, Z. M.; Fahmy, H. H.; Mohamed, H. S. *Arch. Pharm. Res.* **2002**, *25*, 28–38; (e) Singh, N.; Gupta, S.; Nath, G. *Appl. Organomet. Chem.* **2000**, *14*, 484–492; (f) Nakagawa, S.; Otake, N.; Kiyonaga, H.; Yamada, K.; Hona, H.; Ushijima, R. *U.S. Patent* 6,251,891, 2001; *Chem. Abstr.* **2001**, *135*, 61178s.
6. (a) Kanchi, S.; Singh, P.; Bisetty, K. *Arab. J. Chem.* **2014**, *7*, 11–25; (b) Hussein, M. A.; El-Shorbagi, A.-N.; Khallil, A.-R. *Arch. Pharm. Pharm. Med. Chem.* **2001**, *334*, 305–308; (c) Eng, G.; Song, X.; Duong, Q.; Strickman, D.; Glass, J.; May, L. *Appl. Organomet. Chem.* **2003**, *17*, 218–225.
7. (a) Nieuwenhuizen, P. J.; Ehlers, A. W.; Haasnoot, J. G.; Janse, S. R.; Reedijk, J.; Baerends, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 163–168; (b) Messer, W. E. *British Patent* 496560, 1930; *Chem. Abstr.* **1939**, *33*, 4080.
8. (a) Lai, J. T.; Shea, R. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 4298–4316; (b) Dureaault, A.; Gnanou, Y.; Taton, D.; Destarac, M.; Leising, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 2869–2872; (c) Bathfield, M.; D'Agosto, F.; Spitz, R.; Charreyre, M. T.; Delair, T. *J. Am. Chem. Soc.* **2006**, *128*, 2546–2547.
9. (a) Ziyaei Halimehjani, A.; Pourshojaei, Y.; Saidi, M. R. *Tetrahedron Lett.* **2009**, *50*, 32–34; (b) Sugimoto, H.; Makino, I.; Hirai, K. *J. Org. Chem.* **1988**, *53*, 2263–2267; (c) Maddani, M.; Prabhu, K. R. *Tetrahedron Lett.* **2007**, *48*, 7151–7154.
10. Wong, R.; Dolman, S. J. *J. Org. Chem.* **2007**, *72*, 3969–3971.
11. Ziyaei-Halimehjani, A.; Maleki, H.; Saidi, M. R. *Tetrahedron Lett.* **2009**, *50*, 2747–2749.
12. Jamir, L.; Sinha, U. B.; Nath, J.; Patel, B. K. *Synth. Commun.* **2012**, *42*, 951–958.
13. (a) Ziyaei Halimehjani, A.; Marjani, K.; Ashouri, A. *Tetrahedron Lett.* **2012**, *53*, 3490–3492; (b) Ziyaei Halimehjani, A.; Ashouri, A.; Marjani, K. *J. Heterocycl. Chem.* **2012**, *49*, 939–942; (c) Aryanasab, F.; Ziyaei Halimehjani, A.; Saidi, M. R. *Tetrahedron Lett.* **2010**, *51*, 790–792.
14. Ziyaei Halimehjani, A.; Hajiloo Shayegan, M.; Hashemi, M. M.; Notash, B. *Org. Lett.* **2012**, *14*, 3838–3841.
15. Ziyaei Halimehjani, A.; Ranjbari, M. A.; Pasha Zanussi, H. *RSC Adv.* **2013**, *3*, 22904–22908.
16. Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; Wiley Interscience: New York, 1999. 484.
17. (a) Tilles, H. *J. Am. Chem. Soc.* **1959**, *81*, 714–727; (b) Chin-Hsien, W. *Synthesis* **1981**, 622–623.
18. (a) Chaturvedi, D.; Ray, S. *Tetrahedron Lett.* **2006**, *47*, 1307–1309; (b) Azizi, N.; Aryanasab, F.; Saidi, M. R. *Org. Lett.* **2006**, *8*, 5275–5377; (c) Azizi, N.; Ebrahimi, F.; Akbari, E.; Aryanasab, F.; Saidi, M. R. *Synlett* **2007**, 2797–2800; (d) Azizi, N.; Aryanasab, F.; Torkiyan, L.; Ziyaei, A.; Saidi, M. R. *J. Org. Chem.* **2006**, *71*, 3634–3635; (e) Azizi, N.; Pourhasan, B.; Aryanasab, F.; Saidi, M. R. *Synlett* **2007**, 1239–1242; (f) Ziyaei-Halimehjani, A.; Saidi, M. R. *J. Sulfur Chem.* **2005**, 149–154; (g) Ziyaei-Halimehjani, A.; Saidi, M. R. *Can. J. Chem.* **2006**, *84*, 1515–1519; (h) Ziyaei Halimehjani, A.; Marjani, K.; Ashouri, A. *Green Chem.* **2010**, *12*, 1306–1310; (i) Ziyaei Halimehjani, A.; Pasha Zanussi, H.; Ranjbari, M. A. *Synthesis* **2013**, 1483–1488; (j) Yavari, I.; Hosseini, N.; Moradi, L.; Mirzaei, A. *Tetrahedron Lett.* **2008**, *49*, 4239–4241; (k) McGhee, W.; Riley, D.; Christ, K.; Pan, Y.; Parnas, B. *J. Org. Chem.* **1995**, *60*, 2820–2830; (l) Vasiliev, A. N.; Polackov, A. D. *Molecules* **2000**, *5*, 1014–1017; (m) Salvatore, R. N.; Shin, S. I.; Nagle, A. S.; Jung, K. W. *J. Org. Chem.* **2001**, *66*, 1035–1037; (n) Salvatore, R. N.; Sahaba, S.; Jung, K. W. *Tetrahedron Lett.* **2001**, *42*, 2055–2058; (o) Salvatore, R. N.; Ledger, J. A.; Jung, K. W. *Tetrahedron Lett.* **2001**, *42*, 6023–6025; (p) Guo, B. G.; Ge, Z. M.; Cheng, T. M.; Li, R. T. *Synth. Commun.* **2001**, *31*, 3021–3025; (q) Busque, F.; March, P.-D.; Figueredo, M.; Font, J.; Gonzalez, L. *Eur. J. Org. Chem.* **2004**, 1492–1499; (r) Fox, D. L.; Ruxer, J. T.; Oliver, J. M.; Alford, K. L.; Salvatore, R. N. *Tetrahedron Lett.* **2004**, *45*, 401–405; (s) Ranu, B.; Saha, A.; Banerjee, S. *Eur. J. Org. Chem.* **2008**, *3*, 519–523.
19. (a) Makonkawkeyoon, S.; Limsonpobre, R. N. R.; Moreira, A. L.; Schauf, V.; Kaplan, G. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 5974; (b) Figg, W. D.; Raje, S.; Bauer, K. S.; Tompkins, A.; Venzon, D.; Bergan, R.; Chen, A.; Hamilton, M.; Pluda, J.; Reed, E. *J. Pharm. Sci.* **1999**, *88*, 121–125. http://onlinelibrary.wiley.com/doi/10.1021/js980172i/abstract; (c) Al-Soud, Y. A.; Al-Masoudi, N. A. *Pharmazie* **2001**, *56*, 372–375; (d) Henon, H.; Messaoudi, S.; Anizon, F.; Aboab, B.; Kucharczyk, N.; Leonce, S.; Golsteyn, R. M.; Pfeiffer, B.; Prudhomme, M. *Eur. J. Pharmacol.* **2007**, *554*, 106–112.
20. Schwack, W.; Flober-Muller, H. *Chemosphere* **1990**, *21*, 905–912.
21. Sinderhauf, K.; Schwack, W. *J. Agric. Food Chem.* **2003**, *51*, 5990–5995.
22. (a) Linthorst, J. A. *Foundations Chem.* **2010**, *12*, 55–68; (b) Anastas, P. T.; Williamson, T. C. *Green Chemistry: Designing Chemistry for the Environment*; ACS publications: Washington DC, 1996; (c) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford Science Publications: Oxford, 1998;

(d)*Green Chemistry: Frontiers in Chemical Synthesis and Processes*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: Oxford, 1998; (e) Clark, J. H. *Green Chem.* **1999**, *1*, 1–8.
23. (a) Ziyaei-Halimehjani, A.; Ebrahimi, F.; Azizi, N.; Saidi, M. R. *J. Heterocycl. Chem.* **2009**, *46*, 347–350; (b) Ziyaei-Halimehjani, A.; Saidi, M. R. *Tetrahedron Lett.* **2008**, *49*, 1244–1248; (c) Ziyaei-Halimehjani, A.; Aryanasab, F.; Saidi, M. R. *Tetrahedron Lett.* **2009**, *50*, 1441–1443; (d) Ziyaei-Halimehjani, A.; Gholami, H.; Saidi, M. R. *J. Iranian Chem. Soc.* **2013**, *10*, 7–11; (e) Ziyaei Halimehjani, A.; Karimi, N.; Saidi, M. R. *Synth. Commun.* **2013**, *43*, 744–748; (f) Marjani, K.; Khalesi, M.; Ashouri, A.; Jalali, A.; Ziyaei-Halimehjan, A. *Synth. Commun.* **2011**, *41*, 451–458; (g) Ziyaei Halimehjnai, A.; Marjani, K.; Ashouri, A.; Jalali, A. *Synth. Commun.* **2011**, *41*, 1638–1643.
24. Hayashi, Y.; Kayatani, T.; Sugimoto, H.; Suzuki, M.; Inomata, K.; Uehara, A.; Mizutani, Y.; Kitagawa, T.; Maeda, Y. *J. Am. Chem. Soc.* **1995**, *117*, 11220–11229.
25. *Synthesis of N-(2,3-epoxypropyl)phthalimide (**3**):* This compound was synthesized according to the previously reported procedure by refluxing a mixture of potassium phthalimide (6.50 g, 35 mmol) and epichlorohydrin (19.5 mL) at 120 °C for 8 h. The excess epichlorohydrin was removed under reduced pressure to give a yellowish white powder, which was purified by washing with H_2O and recrystallization in MeOH. The pure product was obtained as a white solid in 75% yield (5.3 g); mp 95–97 °C (Lit.[31] mp 98–99 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.68 (1H, dd, J = 4.8 and 2.5 Hz), 2.81 (1H, dd, J = 8.7 and 4.3 Hz), 3.24 (1H, m), 3.80 (1H, dd, J = 14.3 and 4.9 Hz), 3.96 (1H, dd, J = 14.3 and 4.9 Hz), 7.75 (2H,m), 7.86 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 39.6, 46.0, 49.0, 123.4, 131.9, 133.9, 167.9; IR (KBr) 1770, 1713, 1430, 1396, 1043, 724 cm^{-1}; Anal. Calcd. (%) for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89; Found: C, 64.71; H, 4.41; N, 6.87.
26. *General procedure for the synthesis 3-phthalimido-2-hydroxy propyl-1-dithiocarbamates (**4**):* To a mixture of an amine (2.5 mmol) and CS_2 (3 mmol) in H_2O (10 mL), *N*-(2,3-epoxypropyl)phthalimide (**3**) (2 mmol) was added and the mixture was stirred vigorously at room temperature for 8 h. After completion, the products were collected by filtration. In the case of oily compounds, the products were extracted with EtOAc (2 × 10 mL). The combined organic phase was washed with H_2O, and then dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. In most of cases the pure products were obtained without further purification. If needed, the purifications were performed by recrystallization from diethyl ether. It should be noted that in the case of piperazine (2 mmol), CS_2 (6 mmol) and *N*-(2,3-epoxypropyl)phthalimide (**3**) (4 mmol) were used.
27. Ing, H. R.; Manske, R. H. F. *J. Chem. Soc. Abstr.* **1926**, 2348–2351.
28. Osby, J. O.; Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 2093–2096.
29. *Synthesis of 3-amino-2-hydroxypropyl diethylcarbamodithioate (**6**):* To a suspension of 3-phthalimido-2-hydroxy propyl-1-dithiocarbamate (**4f**) (1.5 mmol, 0.528 g) in isopropanol (12 ml) and H_2O (2 ml), $NaBH_4$ (7.5 mmol, 0.28 g) was gradually added and the reaction mixture was stirred at room temperature overnight. The mixture was acidified to pH = 4 with AcOH, warmed to 80 °C, and stirred for 2 h. The volatiles were removed in vacuo, and the resulting solution was diluted with 1 M NaOH and extracted with EtOAc (3 × 10 mL). The combined EtOAc extractions were dried over Na_2SO_4 and evaporated in vacuo, and the residue was purified by column chromatography (silica gel; 1:4 hexane/EtOAc) to give product **6** as a yellow oil (30%, 0.1 g); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.22–1.31 (6H, m), 2.76–2.93 (2H, m), 3.38–3.45 (4H, m), 3.59 (1H, m), 3.73–3.77 (2H, m), 3.87 (1H, m), 3.97–4.01 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 11.6, 12.6, 40.9, 44.6, 45.7, 50.0, 70.4, 195.4; Anal. Calcd. (%) for $C_8H_{18}N_2OS_2$: C, 43.21; H, 8.16; N, 12.60; Found: C, 43.02; H, 8.32; N, 12.44.
30. *Synthesis of N-propylpiperidine-1-carbothioamide (**7**):* Compound (**4i**) (2 mmol, 0.676 g) was mixed with piperidine (3 mmol) and stirred at 80 °C for 8 h under solvent-free conditions. The mixture was extracted with EtOAc (25 mL) and the organic layer was washed with H_2O (20 mL) and 2 M HCl solution. The organic layer was dried and evaporated under reduced pressure to give a viscous residue, which was purified by column chromatography. The thiourea (**7**) was obtained in 50% yield (0.186 g) as a brown viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.88 (3H, t, J = 7.3 Hz), 1.51–1.63 (8H, m), 3.53 (2H, m), 3.71 (4H, m), 5.64 (1H, s); Anal. Calcd. (%) for $C_9H_{18}N_2S$: C, 58.02; H, 9.74; N, 15.04; Found: C, 58.22; H, 9.62; N, 15.24.
31. (a) Pace, V.; Hoyos, P.; Fernandez, M.; Sinisterraa, J. V.; Alcantara, A. R. *Green Chem.* **2010**, *12*, 1380–1382; (b) Heyes, J. A.; Niculescu-Duvaz, D.; Cooper, R. G.; Springer, C. J. *J. Med. Chem.* **2002**, *45*, 99–114.